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Case Report

A case of *Apophysomyces trapeziformis* necrotizing soft tissue infection

Jose F. Echaiz [a,*], Carey-Ann D. Burnham [b], Thomas C. Bailey [a]

[a] *Division of Infectious Diseases, Washington University School of Medicine, 660 S. Euclid, St. Louis, MO 63110, USA*
[b] *Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri, USA*

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SUMMARY

Mucormycosis is a rare and devastating disease. *Apophysomyces trapeziformis* is an environmental mold that was recently implicated in several cases of cutaneous and soft tissue mucormycosis in victims of a tornado in Joplin, Missouri. Here, we report a case of *Apophysomyces trapeziformis* necrotizing soft tissue infection in a resident of Joplin 10 months after the disaster and without preceding trauma. Aspects of histological and microbiological diagnosis are also reviewed.

1. Introduction

Necrotizing cutaneous and soft tissue mucormycosis results from inoculation of fungal spores in the skin, usually from traumatic injuries. These infections carry a high mortality rate and treatment is often challenging.[1] *Apophysomyces elegans* complex is an unusual cause of mucormycosis, representing about 3% of cases reported in the literature.[2] A newly recognized species of this complex, *Apophysomyces trapeziformis*, was involved in 13 cases of necrotizing soft tissue infections after open or blunt trauma in victims of a tornado that struck the city of Joplin, Missouri on May 22, 2011.[3] We report a case of necrotizing soft tissue infection by *A. trapeziformis* in a resident of Joplin presenting 10 months after the tornado and without a history of traumatic injuries.

2. Case report

The patient was a 65-year-old Caucasian woman who had initially presented to a local hospital with a rapidly progressive necrotizing infection that began in the medial aspect of the right arm along with fever. The patient had a past medical history significant for autoimmune hemolytic anemia and immune thrombocytopenia that required a splenectomy in 2011, followed by high-dose corticosteroid therapy that was initiated 4 weeks prior to her presentation. She was treated with broad-spectrum intravenous antibiotic therapy without response. Surgical debridement was performed, and histopathology results from skin and necrotic soft tissue showed the presence of septate broad hyphae branching at 90°, along with foci of necrotizing vasculitis and the presence of branching hyphae invading blood vessel walls. Treatment commenced with liposomal amphotericin B, and two additional surgeries for debridement were performed in the following 48 h. After this, the patient was transferred to our institution. Upon arrival, an emergent repeat surgical debridement was performed and the patient was admitted to the surgical intensive care unit. Surgery revealed extensive necrosis of the soft tissue, biceps muscle, and latissimus muscle. A physical examination did not reveal other areas of skin or soft tissue involvement. The initial laboratory examination was significant for leukocytosis (white blood cell count 18.1×10^9 cells/l), anemia (hemoglobin 8.7 g/dl), and thrombocytopenia (platelet count 65×10^9 cells/l). Bilirubin and transaminases were normal, as was the serum creatinine level. A chest roentgenogram showed lungs free of infiltrates. The patient was treated with intravenous liposomal amphotericin B at a daily dose of 5 mg/kg. Microbiological examination of tissue at our institution showed growth of a zygomycete at 24 h. On the third day of hospitalization, her condition worsened and she developed hypotension and, later on, respiratory failure. Therapy with intravenous vancomycin and meropenem was instituted, but additional diagnostic evaluation failed to reveal another cause for the patient's deterioration. During her hospital stay, the patient underwent three additional surgeries for debridement due to dissemination of the infection towards the chest wall and back as well as vascular structures.

* Corresponding author. Tel.: +1 314 454 8225; fax: +1 314 454 5392.
E-mail address: jechaiz@dom.wustl.edu (J.F. Echaiz).

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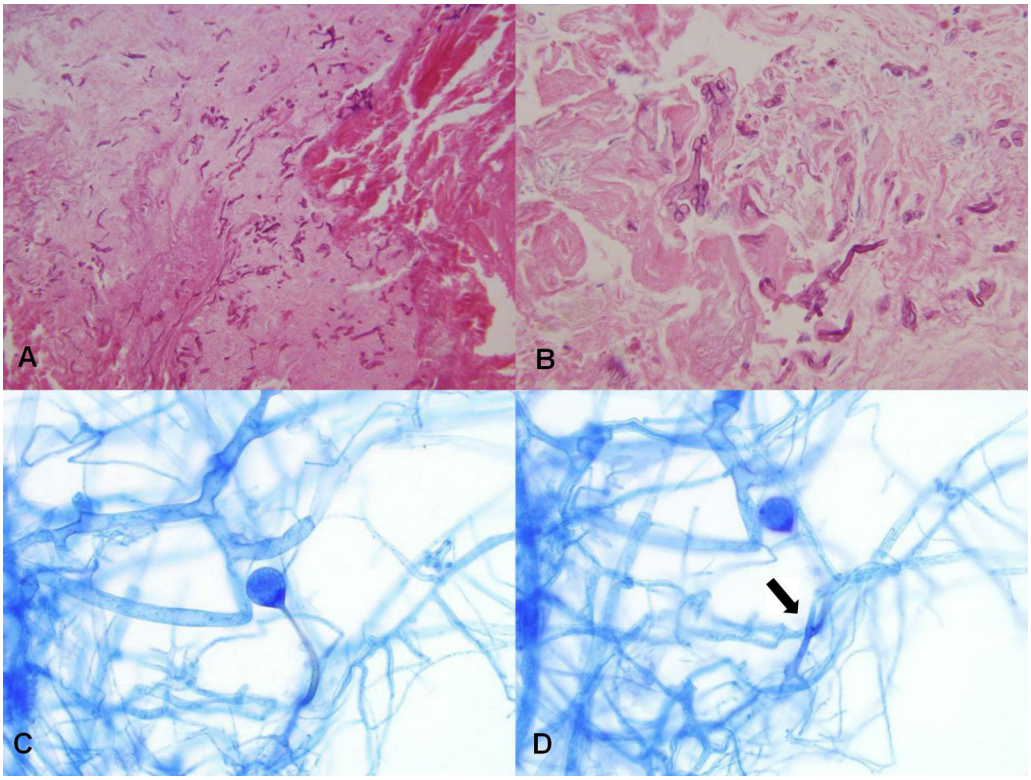

Figure 1. (A) Hematoxylin and eosin stained tissue section depicting fungal elements invading tissue (original magnification, ×100). (B) Haphazard, broad, ribbon-like hyphae with rare to absent septations (original magnification, ×400). (C) Lactophenol aniline blue stain of a tape preparation of the organism cultivated in vitro, following prolonged incubation on potato dextrose agar; hyphae are broad and lacking septations, and the organism exhibits a pronounced apophysis. (D) Presence of 'foot cells' (arrow) at the base of the sporangiophore (original magnification, ×1000).

Tissue samples from the last surgical intervention revealed persistence of fungal elements (broad, ribbon-like hyphae), as shown in Figure 1. Despite combined aggressive medical and surgical care, her condition continued to deteriorate. The patient died on the seventh day of hospitalization. The zygomycete was later identified as *A. trapeziformis* by D1/D2 28S LSU rDNA sequencing performed at the Centers for Disease Control and Prevention. Subsequent whole genome sequencing of this isolate revealed that it was genetically related to other organisms from the Joplin outbreak.[4]

3. Discussion

Apophysomyces trapeziformis is a recently recognized species that was identified as the causative agent of necrotizing soft tissue infections in 13 victims of a tornado in Joplin, Missouri.[3] The infection was associated with traumatic injuries, had a high mortality rate, and affected mainly immunocompetent patients, although two patients had diabetes and one patient had chronic kidney disease. Of note, 100% of the cases were located in the zone of the most severe tornado damage. Our case presented 10 months after the disaster, did not incur any type of traumatic injury, and lived in an area out of the zone of major damage. Although far removed in time from the occurrence of the tornado, whole genome sequencing suggests that our case could have been caused by a strain related to the tornado outbreak. A recent study suggests that *A. trapeziformis* could have been established in the Joplin area previously and that climatic conditions facilitated not only local blooms of the organism but also its dispersion in the tornado area.[4] Interestingly, prior to the use of DNA sequencing and phylogenetic analysis, and prior to the Joplin tornado, there were no published reports of infections by the genus *Apophysomyces* in the Missouri area. Furthermore, published cases of infections by *A. elegans* in the USA have come from Alabama, Arizona, Georgia, North Carolina, and Texas; and no predisposing factor (i.e., trauma) was detected in 15% of all previously reported *Apophysomyces sp* infections.[2] It is possible that an unnoticed trauma was involved in this case, and that it could have allowed inoculation of spores from the environment. Additionally, corticosteroid use and autoimmune or rheumatic diseases, both present in this case, are established risk factors for disseminated forms of mucormycosis, and mortality is particularly high within this population.

The diagnosis of mucormycosis is best attained with a combination of histological and microbiological evidence. Histopathological examination of tissue samples cannot fully distinguish among types of molds and occasionally *Aspergillus* species can resemble zygomycetes on histology, and vice versa. In this case, the initial histological findings were more typical of a zygomycete, with the presence of broad hyphae and 90° branching, but repeat histological examination results at our institution showed features that were considered typical of aspergillosis. Voriconazole is currently the recommended therapy for cutaneous aspergillosis, however in vitro antifungal susceptibility testing for zygomycetes, including *Apophysomyces* species, has shown that voriconazole has less activity compared to amphotericin B or posaconazole.[1] Therefore, microbiological identification by culture or molecular techniques is imperative in the management of suspected mold infections and antifungal choices should not be based solely on histological findings. Similarly, recovery of a zygomycete from clinical specimens is difficult and even after recovery has been successful, identification of species on morphological features alone is difficult, time-consuming, and requires expertise. Apophysomyces is frequently slow to make spores and other diagnostic structures, and in this instance, the

morphologic characteristics necessary to make the identification (Figure 1) required more than14 days of incubation. It is not uncommon that Apophysomyces will not make spores on potato dextrose agar or other primary isolation media commonly used for the cultivation and identification of filamentous fungi.

The treatment of mucormycosis is challenging and requires early surgical debridement as well as proper antifungal therapy. In this case, the treatment approach did not differ from the one used for victims of the Joplin tornado and combination antifungal therapy was not used. Despite promising evidence of improved outcomes of combination antifungal therapy with polyenes and echinocandins for the treatment of rhino-cerebral mucormycosis, the clinical benefit of such a scheme for cutaneous mucormycosis remains to be determined.[5] Also, when considering the use of posaconazole, aspects of its pharmacokinetics and pharmacodynamics may limit its use in certain populations such as critically ill patients. Finally, there is no evidence to support the use of alternative therapies such as hyperbaric oxygen in the management of cutaneous or soft tissue mucormycosis. Nevertheless, if no improvement is observed with amphotericin B, the use of echinocandins could be considered given their benign safety profile and ease of administration.

This case of *A. trapeziformis* necrotizing soft tissue infection illustrates the diagnostic and therapeutic challenges surrounding cutaneous mucormycosis. Although infrequent, mucormycosis must be considered in the differential diagnosis of necrotizing skin and soft tissue infections, even in the absence of trauma or linkage to natural disasters. Early diagnosis with the use of histopathology and microbiological examinations is fundamental to reduce the mortality that accompanies these devastating infections.

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Conflict of interest: There are no competing interests associated with this article.

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